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Synthesis of arylboronates by the palladium catalysed cross-coupling reaction in ionic liquids

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The palladium catalysed cross-coupling reaction of aryl iodides and bromides with pinacolborane in 1,3-dialkylimidazolium tetrafluoroborates and hexafluorophosphates producing arylboronates is described.

Ionic liquids are promising “green” solvents with high potential for organic synthesis.[1] Unique properties, such as negligible vapour pressure, high thermal stability, easy handling, and the ability to dissolve both inorganic and organic compounds, contribute to their increasing applications. Recently, ionic liquids based on 1,3-dialkylimidazolium cations were applied as recyclable reaction media for hydrogenations,[2] the Heck reaction,[3] and the synthesis of biaryls by the Suzuki–Miyaura cross-coupling reaction.[4]

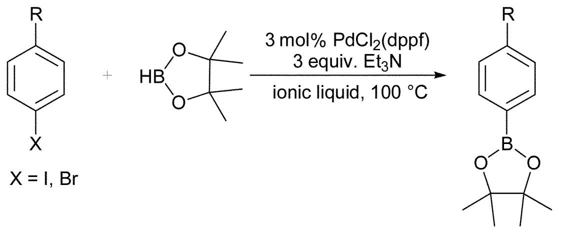
Arylboronic acids and esters (boronates) are highly useful synthetic reagents for the latter reaction.[5] They also exhibit biological activity and are used in molecular recognition processes.[6] Arylboronates can be prepared by the classical transmetallation methodology from arylmagnesium or lithium reagents and trialkoxyboranes.[7] Alternatively, the palladium-catalysed cross-coupling reaction of aryl halides and aryl triflates in molecular solvents with tetraalkoxydiborons,[8] or the more readily available pinacolborane,[9] can be employed. The method tolerates a wide range of functional groups but sometimes suffers from catalyst decomposition and difficulties in product isolation.

Herein, we report the cross-coupling of aryl halides with pinacolborane catalysed with $PdCl_2$(dppf) (dppf = 1,1′-bis(diphenylphosphino)ferrocene) in 1,3-dialkylimidazolium tetrafluoroborates and hexafluorophosphates as solvents (Scheme 1). The reaction of 4-iodoanisole was used to find a suitable solvent, and the yields of **3** are shown in Table 1. The catalytic solution was prepared by heating $PdCl_2$(dppf) (3 mol%) with 4-iodoanisole in an ionic liquid at 100 °C. The solution was then cooled to ambient temperature, triethylamine was added, followed with pinacolborane, and the temperature was raised to 100 °C. GC monitoring showed that the reaction carried out in tetrafluoroborate salts was complete in 20 minutes whereas in hexafluorophosphate salts it took much longer and the yields of products were lower. Catalyst decomposition, indicated by the formation of a black precipitate, was observed in hexafluorophosphate salts and [emim][BF_4]. Colour changes of the reaction mixture are a useful indication of the reaction progress. Thus, a solution of the catalyst and 4-iodoanisole is deep-red. After the addition of pinacolborane and triethylamine the mixture becomes orange, and when the reaction is completed it becomes deep-red again.

Table 1 Synthesis of **3** by the cross-coupling reaction of 4-iodoanisole with pinacolborane at 100 °C in ionic liquids[a]

Ionic liquid[b]	Colour change	Time/h	Yield[c](%)
[emim][BF_4]	+	0.3	82[d]
[bmim][BF_4]	+	0.3	84
[bmim][PF_6]	−	3	66[d]
[hmim][BF_4]	+	0.3	87
[hmim][PF_6]	−	2	77[d]

[a] Catalysed with 3 mol% $PdCl_2$(dppf). [b] emim = 1-ethyl-3-methylimidazolium; bmim = 1-butyl-3-methylimidazolium; hmim = 1-hexyl-3-methylimidazolium. [c] Isolated yield. [d] Catalyst decomposition.



1 2 3 4
R = H; Me; OMe; NO_2

Scheme 1

The reaction of 4-iodotoluene with pinacolborane in [bmim][BF_4], was carried out 10 times using the recycled catalytic solution. The yield of **2** (87%) obtained in the first run decreased only slightly in the last run (82%). The reaction time increased from 20 min for the first run to 2 h in the second and subsequent runs. It should be noted that the purity of pinacolborane is essential for the catalyst stability. When borane–dimethyl sulfide is used for its preparation, the dimethyl sulfide must be completely removed.

The results described above pointed to [bmim][BF_4] and [hmim][BF_4] as convenient solvents. The former was used for further experiments with representative aryl iodides and bromides under the conditions developed for 4-iodoanisole. Thus, iodobenzene, 4-iodotoluene and 4-iodoanisole reacted with pinacolborane within minutes to give the corresponding coupling products **1**–**3** in 80–87% yield (Table 2). In 1,4-dioxane these reactions required 1–2 h affording products in 77–84% yields.[9a] Decreasing the amount of catalyst from 3 to 1 mol% resulted in a longer reaction time, however, the yield remained unchanged (Table 2). 4-Iodonitrobenzene reacted slower presumably due to the effect of the nitro group and low solubility. The use of aryl bromides instead of iodides resulted in partial debromination and lower yields of the coupling products. Colour changes as described above were also observed in the reactions of other aryl iodides, but not bromides (Table 2).

Enhanced palladium catalyst stability in [bmim][BF_4] was observed earlier in the synthesis of biaryls by the Suzuki–Miyaura cross-coupling of aryl iodides and bromides with boronic acids.[4b] More active and stable mixed phosphine and 1-butyl-3-methylimidazol-2-ylidene palladium complexes were identified. Such complexes might be formed in our reactions leading to boron–carbon bond formation, since the same components, [bmim][BF_4], aryl iodide or bromide, and phosphine–palladium complex, are present in the reaction mixture. Active and stable palladium complexes in [bmim][Br] and phosphonium salt ionic liquids have also been observed and isolated.[10,11]

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Table 2 The cross-coupling reaction of aryl bromides and iodides with pinacolborane at 100 °C in [bmim][BF$_4$][a]

Aryl halide	Colour change	Time/h	Product[b]	Yield[c](%)
Iodobenzene	+	0.3	**1**	80
Bromobenzene	−	2	**1**	75
4-Iodotoluene	+	0.3	**2**	87
4-Bromotoluene	−	2	**2**	70
4-Iodoanisole	+	0.3	**3**	84
4-Iodoanisole[d]	+	2	**3**	86
4-Iodonitrobenzene	+	18	**4**	80

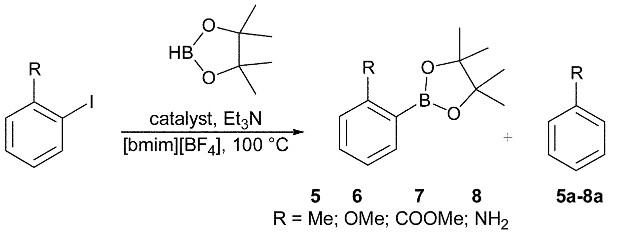
[a] Catalysed with 3 mol% PdCl$_2$(dppf). [b] The products were identified by comparison (^{1}H, ^{13}C, ^{11}B NMR) with the reported spectroscopic data.[9a] [c] Isolated yield. [d] Catalysed with 1 mol% PdCl$_2$(dppf).

Table 3 The cross-coupling reaction of *ortho*-substituted aryl iodides with pinacolborane at 100 °C in [bmim][BF$_4$]

Aryl iodide	Catalyst	Time/h	Products[a] Yield[b](%)			
2-IC$_6$H$_4$Me	PdCl$_2$(dppf)	0.3	**5**	86	**5a**	11
2-IC$_6$H$_4$Me[c]	Pd(OAc)$_2$	6	**5**	88 (82)	**5a**	10
2-IC$_6$H$_4$OMe	PdCl$_2$(dppf)	0.3	**6**	78	**6a**	19
2-IC$_6$H$_4$OMe[c]	Pd(OAc)$_2$	6	**6**	87 (81)	**6a**	10
2-IC$_6$H$_4$COOMe	PdCl$_2$(dppf)	0.3	**7**	25	**7a**	70
2-IC$_6$H$_4$COOMe	Pd(PPh$_3$)$_4$	6	**7**	27	**7a**	68
2-IC$_6$H$_4$COOMe	PdCl$_2$	6	**7**	50	**7a**	46
2-IC$_6$H$_4$COOMe[c]	Pd(OAc)$_2$	6	**7**	70 (62)	**7a**	26
2-IC$_6$H$_4$NH$_2$[d]	PdCl$_2$(dppf)	0.3	**8**	71 (60)	**8a**	24
2-IC$_6$H$_4$NH$_2$[c,d]	Pd(OAc)$_2$	6	**8**	61	**8a**	33

[a] **5**,[9a] **6** and **8**[9c] were identified by comparison (^{1}H, ^{13}C, ^{11}B NMR) with the reported spectroscopic data, **5a**–**8a** and by GC comparison with authentic samples and **7** see note 12. [b] GC yields, by analysis on Supelco SPB-5 column (30 m × 0.32 mm × 0.25 μm) with an internal standard. Isolated yields are given in parentheses. [c] 5 mol% of the catalyst. [d] 2 equivalents of pinacolborane were used.

Recently, it was reported that the PdCl$_2$(dppf) and Pd(OAc)$_2$/2-(dicyclohexylphosphino)biphenyl catalysed cross-coupling reaction of selected *ortho*-substituted aryl iodides with pinacolborane in 1,4-dioxane produced the corresponding boronates in 22–90% yields.[9c] We examined the reaction of representative *ortho*-substituted aryl iodides with pinacolborane carried in [bmim][BF$_4$] in the presence of PdCl$_2$(dppf), and other palladium compounds (Scheme 2). The coupling reactions catalysed with PdCl$_2$(dppf) were completed in 20 min at 100 °C (Table 3). Other palladium compounds required a longer time (6 h) to complete the reaction. Deiodination products were formed in varying amounts depending on the substituent and catalyst. Thus, 10–19% of **5a** and **6a** were obtained from 2-methyl and 2-methoxy derivatives, and 24–70% of **7a** and **8a** from 2-methylcarboxy and 2-amino derivatives. The lowest amount of deiodinated products was obtained in the reactions catalysed by palladium(II) acetate, except the reaction with 2-iodoaniline (Table 3). Colour changes in the reactions catalysed with palladium(II) acetate were less intensive as compared to the reactions catalysed with PdCl$_2$(dppf).



Scheme 2

The coupling products were conveniently isolated by simple extraction of the reaction mixture with petroleum ether. After removal of the solvent, essentially pure products were obtained.[12] The catalyst remains in the ionic liquid and the solution can be used again.

In conclusion, the use of [bmim][BF$_4$] as the reaction medium for the coupling reaction of aryl iodides with pinacolborane is advantageous. The reaction time is shorter as compared to conventional solvents. The product isolation is simple, and it is obtained in good purity directly from the reaction mixture by extraction. A solution of the catalyst in the ionic liquid can be recycled, and colour changes allow easy monitoring of the reaction progress. Partial deiodination is observed in the cross-coupling reactions of *ortho*-substituted aryl iodides. The ratio of coupling products and deiodinated products is influenced both by the substituent and catalyst.

Acknowledgements

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12 Representative procedures: 4,4,5,5-Tetramethyl-2-*p*-tolyl-[1,3,2]dioxaborolane (**2**). 4-Iodotoluene (0.65 g, 3 mmol) was added to a suspension of PdCl$_2$(dppf) (73 mg, 0.09 mmol) in degassed [bmim][BF$_4$] (3 cm^3) under argon atmosphere. The mixture was vigorously stirred at 100 °C, and the deep-red solution was obtained. It was cooled to ambient temperature, triethylamine (0.91 g, 9 mmol) was added, followed by pinacolborane (0.50 g, 3.9 mmol). The mixture was heated at 100 °C with vigorous stirring. The colour changed to orange and after 20 min became deep-red again. The mixture was cooled and extracted with petroleum ether (5 × 10 cm^3). The combined extracts were washed with water (2 × 10 cm^3), and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* afforded **2** (0.57 g, 87% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.34 (s, 12H, CH$_3$), 2.37 (s, 3H, CH$_3$), 7.19 (d, $J = 8.2$ Hz, 2H, CH), 7.71 (d, $J = 8.2$ Hz, 2H, CH); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 21.6 (CH$_3$), 24.8 (CH$_3$), 83.5 (C), 128.5 (CH), 134.8 (CH), 144.3 (C); ^{11}B NMR (64.2 MHz, CDCl$_3$) δ 31.7. The spectral data were identical with the data reported in the literature.[9a] The ionic liquid solution containing the catalyst was dissolved in dichloromethane (10 cm^3), washed with water (3 × 5 cm^3) and dried over anhydrous magnesium sulfate. The solution can be recycled after evaporation of dichloromethane *in vacuo*.

2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)benzoic acid methyl ester (**7**). 2-Iodobenzoic acid methyl ester (0.77 g, 3 mmol) was added to a suspension of Pd(OAc)$_2$ (34 mg, 0.15 mmol) in degassed [bmim][BF$_4$] (3 cm^3) under argon atmosphere. The mixture was vigorously stirred at 100 °C, and a brown solution was obtained. It was cooled to ambient temperature, triethylamine (0.91 g, 9 mmol) was added, followed by pinacolborane (0.50 g, 3.9 mmol). The mixture was heated at 100 °C with vigorous stirring. The colour changed to yellow and after 6 h became brown again. The mixture was cooled and extracted with diethyl ether (5 × 10 cm^3). The combined extracts were washed with water (2 × 10 cm^3), and dried over anhydrous magnesium sulfate. Ether was removed *in vacuo* and the product was isolated by flash chromatography on silica gel (hexane–EtOAc, 9 : 1) (0.49 g, 62% yield); ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.42 (s, 12H, CH$_3$), 3.91 (s, 3H, CH$_3$), 7.41 (m, 1H, CH), 7.51 (m, 2H, CH), 7.94 (ddd, $J = 7.4$, 1.2, 1.0 Hz, 1H, CH); ^{13}C NMR (50.3 MHz, CDCl$_3$) δ 24.8 (CH$_3$), 52.1 (CH$_3$), 83.9 (C), 128.7 (CH), 128.9 (CH), 131.7 (CH), 132.1 (CH), 133.4 (C), 168.4 (C); ^{11}B NMR (64.2 MHz, CDCl$_3$) δ 31.9 (s).